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Remarks

Upon entry of the present amendments, claims 1, 25-27, and 29-69 are pending in this application. Amendments to the claims and new claims (a) effect the elimination of multiple dependent claims, (b) render moot the Examiner's objections alleged improprieties within said multiple dependent claims, and/or (c) render moot other objections of the Examiner. Support for these amendments and additional claims can be found in the application as originally filed and in the claims as originally filed. Claim 28 has been cancelled without prejudice.

It is submitted that no new matter has been introduced by the present amendments and new claims and entry of the same is respectfully requested. By the amendments and cancellation, Applicant does not acquiesce to the propriety of any of the Examiner's rejections and does not disclaim any subject matter to which Applicant is entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997). Further, Applicant reserves the right to prosecute the subject matter of any canceled claim in one or more continuation, continuation-in-part, or divisional applications.

Brief Summary of the Invention

Attorneys for Applicant provide, as a courtesy to the Examiner, the following explanation of one embodiment of the invention described in the pending claims.

The present invention is directed, *inter alia*, to methods of obtaining stem cells from a bloodless source. The present invention completely differs from conventional and known techniques wherein stem cells are obtained from umbilical and placental blood in that, unlike conventional techniques, the cells are *not* obtained from blood. More specifically, these novel cell populations are *not* obtained from the *blood* of an umbilical cord or umbilical vein (collectively "vessels"), nor are the novel cell populations collected from the blood of a placenta.

Attorneys for the Applicant respectfully request that the Examiner turn to Figure 3 (sheet 7 of 8) depicting one example of a stem cell collection system comprising a placenta and vessels. Before any cells are obtained according to methods of the invention, all blood is removed. *See, e.g.*, United States Patent Application Publication No. 2002/0123141 A1 (publication of present application, hereinafter "Application") at ¶ 29. Thus, the tissue is bloodless because it has been drained of all detectable blood; this bloodless state is also termed "exsanguinated." To harvest the cells of the invention a device such as, for example,

a cannula is inserted into one of the placenta's vessels and out of another vessel. Then, according to the example outlined within Figure 3, a solution (perfusate) is circulated through one of the bloodless umbilical cord vessels through the bloodless placenta vasculature and out of the other bloodless umbilical cord vessel.

Applicant postulates (a) that this fluid which is perfused through this stem cell collection system simulates the flow of fluid *in utero* and (b) that this simulation causes the release of otherwise non-recoverable cells (also referred by the inventors as "quiescent cells") to move into the vessels of the tissue and, hence, into the perfusate flowing through the vessels. The release of these cells does not occur immediately at a desirable level. Thus, in one preferred embodiment, the cells are not collected from this perfusate until at least about 4 hours following initiation of flow. In other words, the collection is preferably not begun until perfusate has been flowing through the vasculature of the bloodless tissue for several hours.

The Rejection under 35 U.S.C. § 112, ¶ 1 Should be Withdrawn

The Examiner maintains a rejection of claims 25-46 under 35 U.S.C. § 112, ¶ 1. Final Office Action at pages 2-5. Applicant respectfully traverses. Applicant respectfully requests that the Examiner consider the following arguments in response to the outstanding rejections under 35 U.S.C. § 112, ¶ 1 in light of the Brief Summary of the Invention above.

The Examiner alleges that the phrase "wherein said CD34+ stem cells are not obtained from cord blood" within claim 25 lacks support. *Id.* at page 2. Specifically, the Examiner contends that "the specification is silent with regard to obtaining CD34+ stem cells from a source other than cord blood." *Id.* at page 4. The allegation and contention may stem from a misunderstanding as to the nature of the inventions currently claimed. As Attorneys for Applicant have explained in the summary above, and will explain more specifically below, Applicants are not claiming the isolation of *any* cells of *any* type from umbilical cord *blood* according to the inventions of the present claims.

Applicants wish to bring the Examiner's attention paragraphs 39 and 50 of the Application. These paragraphs describe the isolation of CD34+ cells from the perfusion liquid of the bloodless ("exsanguinated") placenta. Also illustrative is Figure 4 (sheet 8 of 8); this figure exemplifies the isolation of placental CD34+ cells. Attorneys for Applicant further wish to point out that no invention of the current claims involves cells obtained from *blood of any kind*, including cord blood. Thus, the application as filed describes obtaining $CD34^+$ cells only from a source other than cord blood (*i.e.*, the placenta). The recitation "wherein said $CD34^+$ cells are not obtained from cord blood" is therefore fully supported by

the specification. As such, the objection to the amendment filed on 9/8/03, as introducing new matter, is improper. Applicant respectfully requests that the Examiner withdraw this objection.

Additionally, the Examiner contends that "the specification is silent with regard to how to collect placenta stem cells not via umbilical vein and artery." *Id.* at pages 4-5. Without acquiescing to the contention of the Examiner, and solely to promote the progress of the present application, Applicant has amended claim 25 has been amended to incorporate the limitations of cancelled claim 28. Specifically, claim 25 describes methods of collecting $CD34^+$ stem cells from an isolated mammalian placenta comprising, in part, a step of perfusing the placenta with a perfusion solution *wherein the perfusing occurs by passing said perfusion solution into one or both of the umbilical artery and umbilical vein of said placenta.*

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection under 35 U.S.C. § 112, ¶ 1.

The Rejection under 35 U.S.C. § 112, ¶ 2 Should be Withdrawn

The Examiner maintains a rejection of claims 1 and 25-46 under 35 U.S.C. § 112, ¶ 2. Final Office Action at pages 5-7. Applicant respectfully traverses. Applicant respectfully requests that the Examiner consider the following arguments in response to the outstanding rejections under 35 U.S.C. § 112, ¶ 2 in light of the Brief Summary of the Invention above.

The Examiner bases the rejection on the contention that claims 1 and 25-46 are "vague and indefinite." The Examiner appears to believe that references in the present claims to stem cells derived from a placenta (for example, the reference in claim 1 to "placental stem cells") render the "metes and bounds of the claims ... unclear." *Id.* at page 6. Specifically, the Examiner contends that since (a) any population of placental stem cells would allegedly comprise mesenchymal stem cells (*Id.* at page 7) and (b) Minguell et al., 226 EXP. BIOL. MED. 507-20 (2001) allegedly establishes that mesenchymal stem cells are $CD34^-$ (*id.*), the skilled artisan would not know "*what* the cells are," because claim 25 is allegedly "drawn to collecting CD34+ stem cells from an isolated mammalian placenta" (*Id.*).

Applicants have amended claims 1 and 25 to replace with phrase "placental stem cells" with "stem cells from an isolated, exsanguinated placenta" or "CD34+ stem cells from an isolated mammalian placenta," respectively. By this amendment, Applicants remove the specific predicate to the Examiner's rejections on this basis.

Applicant does not disagree with Examiner's apparent characterization of the cells collected in the present method. Like the Examiner, Applicant posits that the placenta comprises many different types of cells (Application at Figure 4, Sheet 8 of 8), all of which may be collected, post-removal of cord blood, by methods disclosed for the first time by the Application. Applicant respectfully traverses, however, the Examiner's contention that the skilled artisan would not know "*what* the cells are." *Id.* The skilled artisan would, in fact, readily understand the limits of the terms "stem cells from . . . a placenta" and "CD34+ stem cells from an isolated mammalian placenta" in view of the Application. These terms (as used in the present claims) refer to those stem cells that are obtained, for example, from a "freshly drained ... placenta" that is (a) "properly stored and drained" (Application at ¶ 20) (b) fully exsanguinated (*Id.* at ¶ 29), and (c) "processed in such a manner as to establish ... an environment in which resident stem cells within the parenchyma and extravascular space are recruited and migrate into the empty microcirculation where [the resident stem cells] can be washed into a collecting vessel by perfusion" (*Id.* at ¶ 15). Thus, the method encompasses the collection of any stem cell, or any $CD34^+$ stem cell, obtainable by the present method from a placenta, but not from blood the placenta may have obtained.

The Examiner rejects claims 26-27, 32, and 36-39 based on the contention that certain limitations lack antecedent basis. Applicant has amended the claims in such a manner as to render this rejection moot.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection under 35 U.S.C. § 112, ¶ 2.

The Objections to the Claim Should be Withdrawn

The Examiner maintains an objection to claims 28, 35-39, and 41-42. Final Office Action at pages 7-8. Applicant respectfully traverses.

In explaining the objection to claim 28 as failing to further limit claim 25, the Examiner states that "claim 28 requires perfusing placenta via umbilical vein and artery, which is the means of collecting core [*sic*, cord] blood as taught in the specification (page 2, 2nd paragraph)." This statement in the specification is background, however, and does not describe the embodiments of the invention as presently claimed. In the method of the invention presently claimed, the placenta is *exsanguinated*; it is impossible to collect cord *blood* from an exsanguinated placenta.[1] Thus, claim 28 did, indeed, limit claim 25 by the

[1] The claimed method claims the recovery of stem cells, not cord blood.

addition of a limitation to specific placement of the cannula. In any event, Applicant has cancelled Claim 28 without prejudice, thus mooting this objection.

In addition, via the claim amendments and new claims, Applicant has rendered the Examiner's objections to claims 35-39 and 41-42 moot.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present objections.

The Rejection under 35 U.S.C. § 103(a) Should be Withdrawn

The Examiner maintains a rejection of claims 1 and 26-46 under 35 U.S.C. § 103. Final Office Action at pages 8-11. Specifically, the Examiner contends that the claims are unpatentable over United States Patent No. 6,461,645 ("Boyse") in view of Belvedere et al., 18 STEM CELLS 2000 245-51 (2000) ("Belvedere"), United States Patent No. 3,862,002 ("Sanders"), and Addison et al., 39(1) J. STEROID BIOCHEM. MOLEC. BIOL. 83-90 (1991) ("Addison"). Applicant respectfully traverses. Further, Applicant respectfully requests that the Examiner consider the following arguments in response to the outstanding rejections under 35 U.S.C. § 103 in light of the Brief Summary of the Invention above.

Boyse allegedly relates to hematopoetic stem and progenitor cells of neonatal or fetal blood that are cryopreserved. In addition, Boyse allegedly suggests the possibility of certain therapeutic uses of such stem and progenitor cells upon thawing. As noted above in the summary of the invention, the pending claims relate, *inter alia*, to methods for the collection of cells from an exsanguinated (*i.e.*, bloodless) placenta. As such, Boyse does *not* teach or suggest the collection of stem cells from a placenta, after exsanguination of the placenta, as claimed in the present application.

The other references cited by the Examiner fail to remedy this critical deficiency of Boyse. Belvedere, like Boyse, allegedly relates to the collection of progenitor cells through an "umbilical cord *blood* collection system" (emphasis added). The Examiner states that "Belvedere et al. teach maximizing the collection of stem cells from the placenta . . ." This is incorrect; Belvedere allegedly teaches collection of stem cells from blood. "From blood" is not the equivalent of "from the placenta"; these tissues are distinct. As noted above, the pending claims do not relate to the collection of cells from blood. In any event, the Examiner has failed to provide, via the references of record, a clear showing of the teaching or motivation to combine Belvedere with Boyse to arrive at the claimed inventions. One of skill in the art would not, therefore, be motivated to combine Boyse and Belevedere to collect stem cells from a source *other* than umbilical cord blood.

Sanders, like Belvedere, fails to remedy the deficiencies of the primary reference. Sanders allegedly discloses a system for the collection of physiologically active placental substances, in which viable placental tissue is placed in a circulating culture medium. The methods allegedly related by Sanders involve (a) the *passive* immersion of placental tissue in a variety of balanced salt solutions and (b) the collection of surface molecules therefrom.[2] In other words, according to the methods allegedly disclosed by Sanders, placental tissue is merely passively bathed in fluid. Sanders also utterly fails to teach how one might collect cells using passive perfusion, much less stem cells post-exsanguination. As such, Sanders does not teach or suggest the methods of the pending claims, *i.e.*, methods that involve (a) the *active* perfusion of solution into and through placental vasculature and (b) the collection of cells from the placenta. Sanders cannot, therefore, remedy the deficiencies of Boyse and Belevedere. The combination of Boyse, Belevedere and Sanders, therefore, fails to teach the collection of placental stem cells according to the claimed invention. This combination therefore does not render the claims obvious.

In addition, at no point has the Examiner provided, via the references of record, a clear showing of the teaching or motivation to combine Sanders with either Boyse or Belvedere to arrive at the claimed inventions. The Examiner states that "it is a well known fact that it is desirable and feasible to maximize the HSC collection by continuous mode of collection . . ." This statement, if true, means that Belevedere cannot be combined with the other references because it teaches the wrong method of perfusion. In fact, it is impossible to perform the claimed method using the technique taught in Belevedere. Apparently to explain this deficiency in Belevedere, the Examiner states that "often times, the cost/efficiency factor takes priority in a clinical setting, thus even though it is obvious that using perfusion would maximize the stem cell collection, perfusion has not been widely used possibly for the cost concern." This assertion, however, is completely speculative, and is not supported by any reference of record.

Applicant asserts that Addison, like Belvedere and Sanders, fails to remedy the deficiencies of the primary reference. Addison allegedly reports an investigation of the placental metabolism of prednisolone (chemically related to hydrocortisone, one of the steroid hormones) by the use of an *in vitro* perfusion technique. Specifically, Addison

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2 Sanders does teach the canulization and perfusion of part of a placenta, the trophoblast. *See* col. 3, lines 49-65. This teaching differs from the claimed invention in two respects. First, the perfusion of the trophoblast is perfusion of only part of the placenta, the outer layer; such perfusion would not reach the entire placenta so as to collect any stem cells therein,. Second, the perfusion taught is only in *preparation* for collection of any placenta-derived substances; the placenta is only thereafter cultured. *See* col. 3, line 66 to col.

reportedly suggests the possibility that, under limited circumstances and via a specific technique, an isolated, perfused human placental lobule may be induced to metabolize a single compound (prednisolone) to other compounds. At no point does Addison teach or suggest the recovery of stem cells from a placenta, let alone any method presently claimed by Applicant, *i.e.*, the isolation of cells post-exsanguination. Indeed, Addison allegedly teaches that the perfusate, once collected, is centrifuged, and that the pellet is discarded; only the supernatant is useful for further work. A person of skill in the art who combines Addison with Boyse, and/or Belevedere and Sanders therefore could never achieve the object of the invention—the collection of placental stem cells.

The Examiner essentially argues that one would be motivated to combine references that do not teach the collection of placental cells, with a reference that teaches discarding cells in perfusates, to arrive at the claimed invention, directed to the collection of placental cells in perfusates. Given this, the Examiner has failed to demonstrate, via the references of record, that one of ordinary skill in the art would have been motivated to combine Addison with any one or any combination of Boyse, Belvedere, and Sanders to arrive at the claimed inventions.

Placing Boyse, Belvedere, Sanders, and Addison aside, the Examiner also makes several sweeping, unsuported statements regarding the alleged knowledge of one of ordinary skill in the art. Specifically, the Examiner contends that it would have been obvious to one of ordinary skill in the art at the time of the invention "to modify the methods taught [by the cited references] by combining or substituting the pressure device with the perfusion in collecting placental stem cells with a reasonable expectation of success." Final Office Action at page 10. The Examiner also contends, for example, that "it is a well-known fact that it is desirable and feasible to maximize [stem cell] collection by a continuous mode of collection." *Id.* Given that these statements are not supported by the references of record, Applicant is improperly denied the opportunity to adequately rebut these statements. To the extent that the Examiner desires to maintain these statements as a basis for the rejection under 35 U.S.C. § 103, Applicant respectfully requests that the Examiner support the allegations by rendering of record either a reference or an affidavit supporting the allegations subject, of course, to examination and rebuttal by Applicant.

For the reasons outlined above, Applicant respectfully requests reconsideration and withdrawal of the present rejection under 35 U.S.C. § 103.

4, line 30. Thus, this aspect of Sanders does not teach a method of perfusion combinable with the remainder of

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The Nonstatutory Double Patenting Rejection

Applicant appreciates the Examiner's holding of this rejection in abeyance until such time as relevant claims of the instant application and co-pending United States Patent Application No. 10/074,976 are allowed. Final Office Action at page 12.

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the cited art to render the claimed method obvious.

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CONCLUSION

Applicant respectfully requests that the above remarks and accompanying documents be entered in the present application file. An early allowance of the present application is respectfully requested.